yield a substantially nonlethal SPE–C, Applicants have met several descriptions of the standard for enablement under § 112, first paragraph.

The Standard for Enablement as Stated by the Federal Circuit and Described in the MPEP

The MPEP provides one statement of the standard for enablement at § 2164.08, which reads:

> Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).
>
> As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971).
> ...
>
> How a teaching is set forth, by specific example or broad terminology, is not important. In re Marzocchi, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). ... In In re Goffe, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976), the court stated:
>
> > [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.
>
> M.P.E.P. at 2164.08.

The MPEP describes that claims must have a reasonable correlation with the specification, must be commensurate in scope with the specification, can be provided either by specific examples or broad terminology, and cannot be limited to the preferred or exemplified embodiments. Applying this standard leads to the conclusion that the present claims are enabled.

The Present Claims are Enabled According to The Standard of the MPEP and Federal Circuit

The MPEP indicates that "the scope of enablement must only bear a 'reasonable correlation' to the scope of the claims." In this case, the claims relate to a mutant SPE–C toxin that is substantially nonlethal. The entire protein consists of only 235 amino acids. The specification specifically recites 16 secondary structural features of this relatively small protein that are suitable locations for mutations yielding a nonlethal protein. Further, the specification

explicitly calls out 39 amino acid residues of this relatively small protein that are suitable sites for mutation. This detailed disclosure of features and residues that can be mutated in SPE–C reasonably correlates with the scope of the present claims. Therefore, Applicants are entitled to a claim that broadly describes a nonlethal SPE–C mutant and includes each of these 16 secondary structural features and 39 amino acid residues. Claims 1–17 are such claims. Thus, the present disclosure meets the standard for enablement as described in the MPEP at § 2164.08 and in In re Fisher.

The MPEP further states that the only relevant concern is whether the disclosure provides a scope of enablement commensurate with the scope of the claims. Again, the present disclosure specifically recites 16 secondary structural features and explicitly calls out 39 residues of a relatively small protein as sites that are suitable for mutation. This extensive description of suitable regions of the protein is disclosure commensurate with the scope of claims to mutations throughout the protein. Therefore, Applicants are entitled to a claim that broadly describes a nonlethal SPE–C mutant and includes each of these 16 secondary structural features and 39 amino acid residues. Claims 1–17 are such claims. Thus, the present disclosure is enabling according to the standard expressed in the MPEP at 2164.08 and in In re Moore supra.

The MPEP notes that an enabling disclosure can include either specific example or broad terminology. The present application includes working examples demonstrating the production of specific nonlethal SPE–C mutants, provides specific description of 16 secondary structural features that are suitable sites for mutations, and explicitly calls out 39 amino acids preferred as residues to be mutated. Therefore, Applicants are entitled to a claim that broadly describes a nonlethal SPE–C mutant and includes each of these 16 secondary structural features and 39 amino acid residues. Claims 1–17 are such claims. Thus, the present disclosure meets the standard for enablement as described in the MPEP at 2164.08 and in re Marzocchi.

The MPEP also notes that limiting an inventor to claims to preferred materials or what the inventor has found will work does not serve the constitutional purpose of promoting progress in the useful arts. In the present case, Applicants have exemplified several nonlethal mutants of SPE–C, have explicitly described 39 amino acids that are preferred sites for making such mutants, and specifically describe 16 secondary structural features that are suitable locations for mutations eliminating toxicity. By the standard expressed in In re Goffe and in the MPEP at 2164.08, constitutional purposes would be defeated by limiting the inventor to the specifically

disclosed mutants of SPE–C. Thus, the inventors are entitled a generic claim including all of these nonlethal mutants of SPE–C.

The MPEP then continues in § 2164.08 with examples from court cases applying the enablement standard to biotechnological inventions. The MPEP discusses the Amgen case in which Amgen claimed many DNA sequences encoding analogs of a protein, but told how to make and use only a very few of them. The claims of the present application cover only a finite number of nonlethal mutants of SPE–C; and the present specification specifically describes 16 secondary structural features of the protein that are suitable locations for these mutations and explicitly calls out 39 amino acids that are preferred residues for mutation. The present application tells how to make and use a wide variety of mutants and enables a broad claim including all of these mutants. This presents another example of how the present application meets the standard for enablement as expressed in the MPEP at 2164.08. A similar analysis applies to show enablement in the present application compared to the other specific examples of biotechnological inventions described in the MPEP at 6164.08. Therefore, Applicants are entitled to a claim that broadly describes a nonlethal SPE–C mutant and includes each of these 16 secondary structural features and 39 amino acid residues. Claims 1–17 are such claims.

Further, the MPEP at 2164.08 states that:

> If a rejection is made based on the view that the enablement is not commensurate in scope with the claim, the Examiner should identify the subject matter that is considered to be enabled. MPEP at 2164.08.

Applicants respectfully request that the Examiner provide such an indication of subject matter that is considered to be enabled.

Applicants' specification need not specifically describe how to obtain each and every nonlethal mutant of SPE–C. Applicants' invention is enabled even if it requires some experimentation to make some of the nonlethal SPE–C mutants. The necessity of some experimentation does not preclude enablement under § 112, the key is whether the experimentation is undue. In re Angstadt at 218–219. Even a considerable amount of experimentation is permissible if it is merely routine, or if the specification provides reasonable guidance with respect to the direction the experimentation should proceed. Ex parte Jackson, 217 USPQ 804, 807 (Bd. App. 1982).

Applicants provide more than reasonable guidance regarding the direction in which experimentation should proceed. For example, Applicants provide a lengthy and specific

description of structural features and amino acid residues that are suitable sites for mutations in SPE–C (specification including at page 11, line 12–page 17, line 5). Preferred amino acid substitutions are described in the specification at least at page 9, lines 17–31 and in original claims 4 and 5). Although methods for producing mutant proteins are well known to those of skill in the art, methods for making mutants are disclosed in the specification at least at page 10, lines 1–29; page 25, line 29 through page 32; and in Examples 5 and 6 at pages 35–39. Well known and routine methods for determining the nonlethal nature of a SPE–C mutant are described in the specification at least at page 17, line 5 through page 18, line 2; and in Examples 3, 4, and 6. The specification provides the key information of the features and residues on SPE–C that can provide nonlethal mutants. Those mutants can be made and evaluated by methods that are routine and that are described in the patent application. The fact that mutants would have to be made and assayed for lethality to determine whether a given SPE–C mutant is within the scope of the claims does not constitute "undue experimentation", particularly in an art where the level of skill is so high. In re Wands, 858 F2d 731 at 739 (Fed. Cir. 1988). Therefore, according to the standards of In re Angstadt, Ex parte Jackson, and In re Wands, the present claims are enabled.

Not only does the present application specifically identify particular regions and residues of SPE–C that are suitable for mutation, it provides working examples detailing success in producing several nonlethal SPE–C mutants. The examples describe 12 SPE–C mutants that were made and evaluated. Four of the twelve were tested for lethality; none of them were lethal. That is, 100% of the mutants reported in the present application that were tested for lethality were nonlethal.

In addition, since filing the present application, Applicants have employed the method described in the present patent application to produce an additional five SPE–C mutants. These studies are described in a Declaration Under 37 C.F.R. § 1.132 by Dr. Schlievert, one of the present inventors, to be submitted within a week after submission of this Amendment. Each of these mutations is at a residue specifically identified in the patent application. Four of the five (80%) of the mutants were completely nonlethal; the remaining mutant exhibited reduced lethality. These combined results demonstrate that Applicants achieved success in at least eight of nine (89%) of trials of the method described in the present application.

The high success rate achieved by following the teachings of the present specification fits several standards for enablement. First, this high level of predictability fits the criteria of Ex

parte Forman, (230 USPQ 546 (BPAI 1986)), which refers to " the predictability or unpredictability of the art". Clearly at an 89% success rate Applicants are working in a predictable art. The success rate of 89% using the teachings of Applicants' application also fits a standard for enablement established by the Court of Appeals for the Federal Circuit. In re Wands, *supra*. In the Wands case the Federal Circuit has found enablement when a method had a success rate of only 44%, which is well below the 89% rate achieved by Applicants. Thus, according to the standard of Wands, Applicants' specification is enabling.

Thus, Applicants have met several different standards for demonstrating that the claimed mutants are enabled. First, the high success rate with which Applicants have made nonlethal mutants indicates that the specification enables a broad claim reciting nonlethal mutants. Second, Applicants' specification meets standards of enablement established by the Patent Office and the Federal Courts. Therefore, Applicants' disclosure of numerous specific regions and residues suitable for making nonlethal SPE–C mutants, together with their 89% success rate in making such mutants, provides enabling basis for a claim including all of these mutants, such as present claim 1, and its dependent claims 2–17.

Enablement of Vaccine Claims

The Examiner asserts that the application must provide additional information regarding protective immunity achieved with the claimed vaccines. Applicants respectfully submit that the application sufficiently describes mutants that achieve protective immunity. For example, the specification reports experimental results demonstrating that two of two mutants tested achieved protective immunity, a 100% success rate. After filing of the present application, Applicants produced and tested an additional two mutants, both of which demonstrated protective immunity, maintaining Applicants 100% success rate. Further, as described above, Applicants provide extensive guidance in their application regarding the successful production of nonlethal SPE–C mutants. The specification also describes routine and simple methods by which these nonlethal mutants can be tested for success in inducing protective immunity. These routine methods are described in the specification at least at page 18, lines 3–11 and in Example 6. Therefore, for all of the reasons stated above, Applicants respectfully submit that the present specification fully enables claims to nonlethal SPE–C mutants and vaccines including these mutants.

Protein Structure References Cited by the Examiner

In this rejection, the Examiner cites several references dating between 1984 and 1991 to support assertions regarding protein stability. Applicants respectfully submit that the state of the art for determining and analyzing protein structures between 1984 and 1991 is not relevant to enablement of the present application. The present application claims priority to a filing date in December 1996. Enablement of the present application should be judged based on the state of the art regarding mutant proteins as of this December 1996 filing date. The protein arts advanced considerably between 1991 and December 1996, and especially between 1984 and December 1996. For example, it was only after 1991 that x–ray crystallography became a routine method for determining protein structures, and modeling studies of three dimensional structures of proteins also advanced in that time period. Therefore, Applicants respectfully submit that it is inappropriate to depend on teachings of these old articles and books to support an enablement rejection. Applicants respectfully request the Examiner withdraw the comments regarding these references and the rejection based on these references.

Protein Stability

The Examiner's rejection includes a paragraph questioning whether the claimed mutants of SPE–C would be stable. Applicants are uncertain of the relevance of this paragraph.

The claims make no recitation regarding the stability of the mutant SPE–C toxin. Therefore, it is believed that questioning the stability of the mutant is inappropriate. The claims do recite that the protein is substantially nonlethal, and the specification provides abundant teaching regarding mutations that achieve this desired nonlethality. A nonlethal protein that gives rise to a protective immune response is sufficiently stable to be employed in a vaccine. No test for stability is required.

Applicants respectfully request either clarification or withdrawal of the Examiner's comments regarding stability of the SPE–C mutants.

Conclusion

In conclusion, based on the above, Applicants respectfully submit that the claims are fully enabled by the specification as filed. Applicants respectfully request withdrawal of this rejection.

Rejection of Claims Under § 112, Second Paragraph

The Examiner rejected claims 1–16 under 35 U.S.C. § 112, second paragraph. The Examiner objected to certain terms and phrases employed in the claims. Applicants respectfully traverse this rejection.

The Examiner suggested spelling out the words forming the acronym SPE–C the first time its used in a claim. Claim 1 has been amended as suggested by the Examiner.

The Examiner objects to the recitation in claim 1 of the phrase "substantially nonlethal". Applicants respectfully direct the Examiner's attention to the specification as filed at page 17, lines 5–12. This passage describes that the claimed mutant SPE–C toxins are substantially nonlethal in rabbits when administered by miniosomotic pump (as described in Example 4) at the same or greater dose than a wild type SPE–C toxin. Specifically, the mutant SPE–C is substantially nonlethal if when administered to a rabbit at the same dose as the wild type toxin, less than about 10–20% of rabbits die. Id. Applicants respectfully submit that the phrase "substantially nonlethal" is clearly defined by the specification.

The Examiner noted inadvertent typographical errors in the numbering of certain amino acid residues in the specification at pages 11 and 12 and in Table 2. Applicants have corrected these inadvertent typographical errors by the present amendment to the specification. Applicants note that the specification clearly states that numbering of amino acid residues is made by reference to the sequence of Figure 1 (specification at page 7, lines 13–16). The amendments to the specification bring the text into accord with the sequence numbering in Figure 1.

The Examiner objected to the recitation in claim 10 of the phrase "substantially enhanced endotoxin shock". Applicants respectfully direct the Examiner's attention to the specification at least at page 19, lines 7–15. This passage describes that a lack of enhancement of endotoxin shock can be evaluated in rabbits as described in Example 3. Substantially no enhancement of endotoxin shock is seen when less than about 25% of the animals develop shock when the mutant SPE–C toxin is co–administered with endotoxin as compared to wild type SPE–C activity at the same dose. Preferably, substantially no enhancement of endotoxin shock results in none of the animals developing shock. Id. Therefore, Applicants respectfully submit that the phrase "substantially enhance endotoxin shock" is well defined in the specification as filed.

The Examiner objected to the recitation of "reducing symptoms" in claim 16. Claim 16 has been amended to describe that the vaccine can reduce one or more symptoms. The Examiner asserts that one of skill in the art would not clearly understand reducing symptoms of toxic

shock. First, the specification discloses that symptoms of toxic shocks are well known (specification at page 1, lines 19–28). Specific symptoms are also described in the specification at least at page 25, lines 16–19 and at page 35, lines 17–19. A clinician skilled in the art of reducing symptoms of toxic shock would clearly comprehend the nature of reduced symptoms. Therefore, Applicants respectfully submit that this recitation in the claims is well defined.

Accordingly, it is believed that the claims fully comply with § 112, second paragraph, and withdrawal of this rejection is respectfully requested.

Rejection of Claims Under § 102

The Examiner rejected claims 1 and 13–14 under 35 U.S.C. § 102(b) as anticipated by *Goshorn et al.* (Infection and Immunity 56 (9):2518–2520 (1988)). Applicants respectfully traverse this rejection.

The standard for anticipation requires that a single document disclose every element of a claim. The *Goshorn et al.* reference fails to disclose any mutants of SPE–C, much less any substantially nonlethal mutants of SPE–C. This reference merely discloses the amino acid sequence of the wild type SPE–C. Therefore, the *Goshorn et al.* reference cannot anticipate the presently claimed invention.

The Examiner cites the *Goshorn et al.* reference for its description of "deletion subclones" employed to clone and sequence the wild type SPE–C (*Goshorn et al.* at page 2518, paragraph bridging columns 1 and 2). Applicants are uncertain how the creation of deletion subclones while cloning and sequencing a gene for wild type SPE–C relates to the present claims. Applicants respectfully submit that deletion subcloning refers to a procedure in which the ends of a large piece of DNA are trimmed away to provide a smaller piece of DNA with an intact coding sequence. Each of these deletion subclones included an intact SPE–C wild type coding sequence. Thus, such a procedure does not produce a DNA sequence that might fall under claim 13 or 14 of the present application. The Declaration Under 37 C.F.R. § 1.132 by Dr. Schlievert (to be submitted within a week after submission of this Amendment), one of the present inventors and an author of the *Goshorn et al.* reference, states that this was the type of deletion subcloning conducted. Further, deletion subcloning does not produce any proteins. Therefore, this procedure does not produce a protein that might fall under claim 1 of the present application.

The Examiner asserts that the *Goshorn et al.* reference suggests using site directed mutagensis to analyze the SPE–C toxin. Applicants respectfully note that the *Goshorn* reference states "Future studies will utilize site–specific mutagenesis to analyze such regions." (*Goshorn et al.*, page 2519, column 2, last sentence of first full paragraph). That is, the *Goshorn et al.* reference states that it would be desirable to continue studies employing a technique commonly used for characterizing proteins. No such mutant was made, and no structure of any such mutant is described. Therefore, this recitation does not teach any SPE–C mutant or a sequence encoding that mutant. The Examiner's logic in employing this passage would require that any mutant of any coding sequence or protein would be obvious based on knowledge of the wild type sequence and the existence of the technique of site directed mutagenesis. Such logic is not in accord with the patent law.

The Examiner then goes on to describe that the *Goshorn et al.* reference discusses similarities between the SPE–C amino acid sequence and amino acid sequences of other toxins. *Goshorn et al.*, however, fail to mention even a single hypothetical mutant of SPE–C. Therefore, this discussion fails to teach any aspect of the present claims.

The *Goshorn et al.* reference cited by the Examiner describes the sequence of a wild type SPE–C protein and the DNA encoding it. This reference suggests that it might be desirable to study this protein through site–specific mutagenesis. The reference fails to mention even a hypothetical mutant of either the SPE–C protein or DNA encoding such a mutant. Therefore, this reference cannot anticipate any claim of the present application.

Accordingly, based on the foregoing differences, it is respectfully submitted that the reference applied by the Examiner neither teaches nor suggests the presently claimed invention, and withdrawal of this rejection is respectfully requested.

Rejection of Claims Under § 103

The *Goshorn et al.* and *Kline et al.* References

The Examiner rejected claims 1–10 and 13–14 under 35 U.S.C. § 103(a) as obvious over *Goshorn et al.*, in view of *Kline et al.* Applicants respectfully traverse this rejection.

As discussed above for the anticipation rejection, the *Goshorn et al.* reference neither teaches nor suggests the presently claimed mutant SPE–C, vaccines or compositions including these mutants, a sequence encoding these mutants, or methods employing the mutants. The *Kline et al.* reference does not remedy the shortcomings of the *Goshorn et al.* reference.

First, the *Kline et al.* reference is not properly considered as prior art against the present application. The *Kline* reference was published in March of 1996, which is less than one year before the priority date of the present application, December 6, 1996. Applicants will submit within a week after submission of this Amendment a Declaration Under 37 C.F.R. § 1.131 by Dr. Patrick Schlievert stating that the presently claimed invention was developed before the publication date of the *Kline et al.* reference. Therefore, the *Kline et al.* reference is not properly considered as prior art against the present application.

Further, even if it were prior art against the present application, the *Kline* reference does not remedy the shortcomings of the *Goshorn et al.* The *Kline et al.* reference discloses residues of the SPE–A toxin that are said to be important to T–cell mitogenicity and for class II MHC binding. It is believed that portions of the SPE–C protein relevant to these biological activities are not necessarily relevant to lethality (present specification at paragraph bridging pages 17–18). The present application describes complex and detailed modeling studies done with the SPE–C molecule to determine secondary structural features and residues that are important for producing a nonlethal SPE–C mutant. There is no suggestion or even mention in the *Kline* reference of how a skilled worker might accomplish such modeling to discover such structural features and residues, or of any other way to develop a nonlethal SPE–C mutant. Therefore, the *Kline et al.* does not remedy the deficiencies of the *Goshorn et al.* reference, and does not provide any teaching or suggestion of the presently claimed invention.

Accordingly, the combined references cited by the Examiner neither teach nor suggest the presently mutants, vaccines, pharmaceutical compositions, DNA sequences, transformed host cells, or methods, and withdrawal of this rejection is respectfully requested.

The *Goshorn et al.* and *Leung et al.* References

The Examiner rejected claims 11–12 and 15–16 under 35 U.S.C. § 103(a) as obvious over *Goshorn et al.* in view of *Leung et al.* Applicants respectfully traverse this rejection.

For the reasons described above, the *Goshorn et al.* reference neither teaches nor suggests the presently claimed invention. The *Leung et al.* reference does not remedy the shortcomings of the *Goshorn et al.* reference.

The Examiner cites the *Goshorn et al.* reference for disclosure of the sequence of the wild type SPE–C protein. The *Leung et al.* reference is cited for the broad proposition that a mutant of a protein can be employed to elicit an immune response that is protective against a pathogenic

microorganism. *Leung et al.* propose employing a mutated toxin protein, TSST−1, to elicit a protective immune response against a bacteria that produces this protein. Of course, employing altered materials derived from a pathogenic microorganism is one of the oldest methods for making vaccines, and the *Leung et al.* reference merely applies this tried and true method to a particular microorganism.

The logic employed by the Examiner in this rejection would make obvious any vaccine, pharmaceutical composition, or method of treatment employing an altered natural substance. The Examiner's logic seems to say that the existence of a substance together with the traditional method for making vaccines by employing an altered version a substance makes obvious any vaccine employing the altered substance. Thus, the Examiner's logic would make vaccines unpatentable as obvious over the existence of the natural substance and a traditional method for making vaccines. Applicants respectfully submit that this logic is flawed and that it is well known that vaccines are patentable.

The present claims to a vaccine, pharmaceutical composition, or method employing a mutant SPE−C are not made obvious by a reference disclosing the structure of the wild type SPE−C together with a reference disclosing employing an altered material from a microorganism as a vaccine against that microorganism. Therefore, the references cited by the Examiner do not make obvious any of the present claims.

Accordingly, based on the foregoing differences, it is respectfully submitted that the combined references cited by the Examiner neither teach nor suggest the claimed vaccines, pharmaceutical compositions, or methods, and withdrawal of this rejection is respectfully requested.

Summary

In summary, each of claims 1–17 are in condition for allowance.

The Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below, if the Examiner believes that doing so will expedite prosecution of this patent application.

Respectfully submitted,

MERCHANT & GOULD P.C.
3100 Norwest Center
90 South Seventh Street
Minneapolis, Minnesota 55402
(612) 332–5300

Date: March 6, 2000

Mark T. Skoog

Mark T. Skoog
Reg. No. 40,178
MTS:PSTkaw